Evaluation of Phage Therapy for the Treatment of Burn Wound Infection

PhagoBurn Back to the Phuture

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PHERECYDES PHARMA

Disclosure and grants

The opinions or assertions contained herein reflect the positions of Pherecydes Pharma Co.

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Official announcement

PhagoBurn phase I/II clinical trial has been kicked off.

It targets 3rd degree burn wounds infected by *E. coli* or *P. aeruginosa*.

Belgium and France gave their approval on June 24 and Switzerland on July 7, 2015

The first patients have been already included.

[1]A Trade Mark from Iuliia Faidiuk

The SME singers

- Sponsor of the trial and co-coordinator of the project:
  - Hélène Blois, Guillaume l'Hostis, Aurélie Marchet, Mathieu Medina, Léna Falconet, Meriem Mekrouti, Patrick Champion-Arnaud and Flavie Pouillot (previous R&D Manager)
- Manufacturing of phages under GMP conditions:
  - Laurent Bretaudeau, Isabelle Arnaud, Audrey Larrieu, Olivier Boisteau, François Pedelaborde, Karine Tremblais…
- Administration of the clinical trial:
  - Goulven Theze, Christine Cotton (statistician), Lise Mercatti
- Administration/finances of the Phagoburn project:
  - Olivier Degrand, Delphine Chatard

The rocking clinicians

FRANCE	**Dr. Patrick JAULT (coordinator) & Prof. Thomas LECLERC**	Instruction Military hospital Percy – Paris (Clamart)
SWITZELAND	**Dr. Yok Aie QUE**	CHUV - Lausanne
BELGIUM	**Dr. Serge JENNES**	Hôpital militaire Reine Astrid Bruxelles
FRANCE	**Dr. François RAVAT**	Centre hospitalier Saint Joseph Saint Luc - Lyon
FRANCE	**Dr. Ronan LEFLOCH**	CHU - Nantes
BELGIUM	**Dr. Anne-Françoise ROUSSEAU**	CHU - Liège
BELGIUM	**Dr. Jean-Philippe FAUVILLE & Dr. Ghüder SAIDANE**	Hôpital de Charleroi - Loverval
FRANCE	**Dr. Hervé CARSIN**	Centre Hospitalier Hôpital de Mercy Metz-Thionville
FRANCE	**Dr. Sandrine Wiramus**	Hôpital de la Conception – APHM Marseille
FRANCE	**Dr. Nathalie Bénillan**	Centre FX Michelet CHU Bordeaux
FRANCE	**Dr. Eric Meaudre**	Hôpital d'instruction des armées Sainte-Anne - Toulon

PRINCIPAL INVESTIGATOR

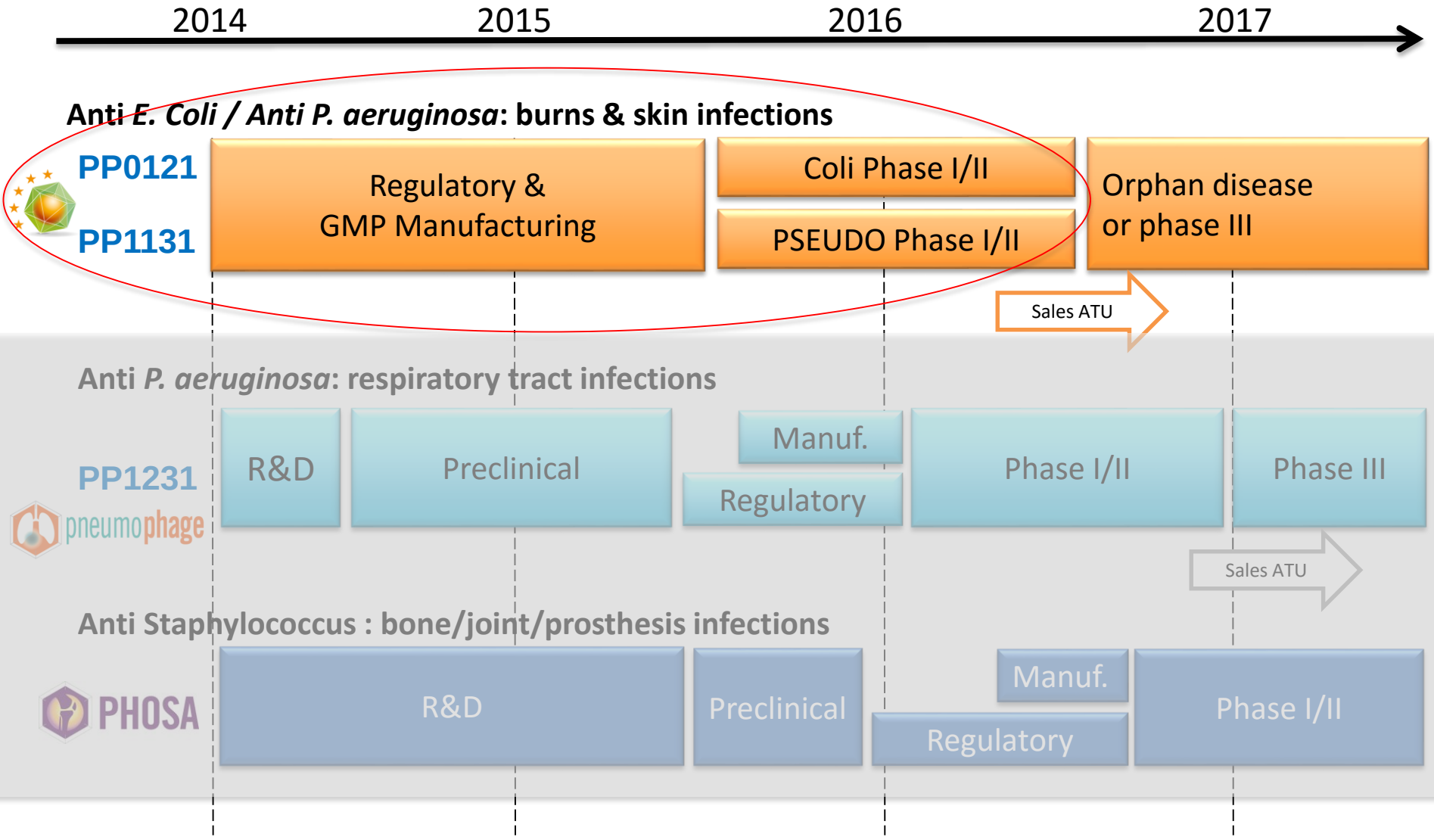
Service de Santé des Armées

The theater Managers

- French medicinal agency
  - For Clean Cells certification as Pharmaceutical Laboratory
  - For Good Manufacturing Practices support and inspection
  - For clinical trial approval in France after Ethical Committee
- Belgium medicinal agency
  - For clinical trial approval in Belgium after EC
- Swiss medicinal agency
  - For clinical trial approval in Swiss after EC
- European Medicines Agency
  - For Working on the evolution of the European pharmacopeia toward phage therapy


THE GEAR

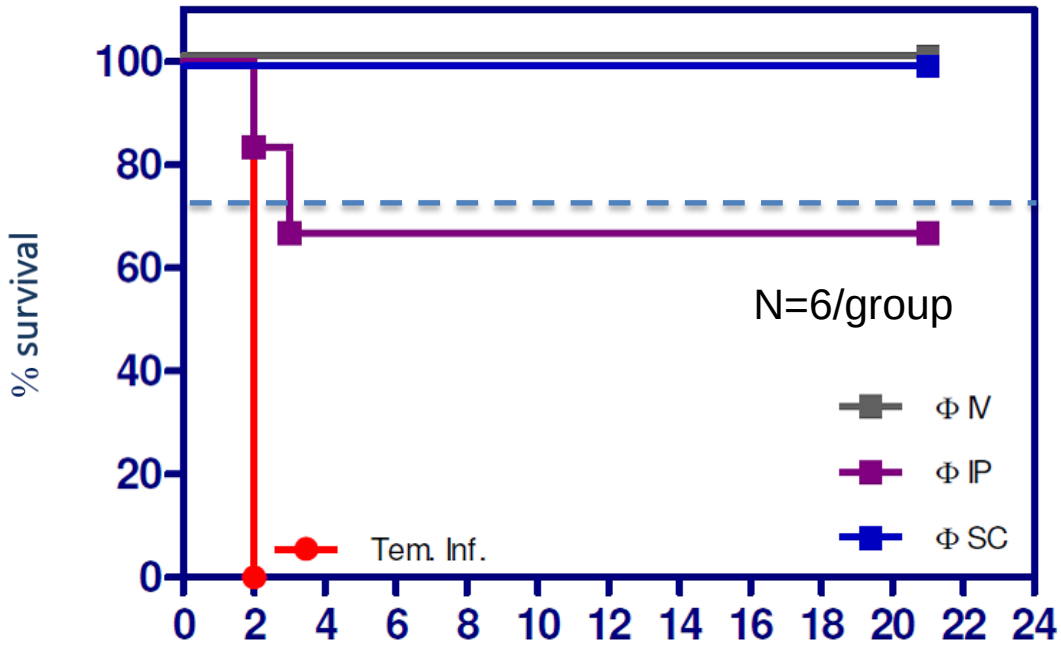
The products



PP0121 efficacy on infected burns

Routes of administration in a mice model

Day	-3	-2	-1	0	1
Treatment	Immuno supression	Yperite burn	Immuno supression	Bacterial challenge MDR ESBL SH113 *E. coli*	Immuno supression
Mode	IP	SC	IP	**SC (10^7cfu)**	IP
PHAGES (10^8 pfu/ml)				SC, IV or IP 6h post-infection	



Gentamycin 6h post-infection:
2x on D1, D3-8 & 4x on D2

70% (IP) to **100% survival** (SC or IV)

PP0121 efficacy on infected burns

Role of the dose in a mice model

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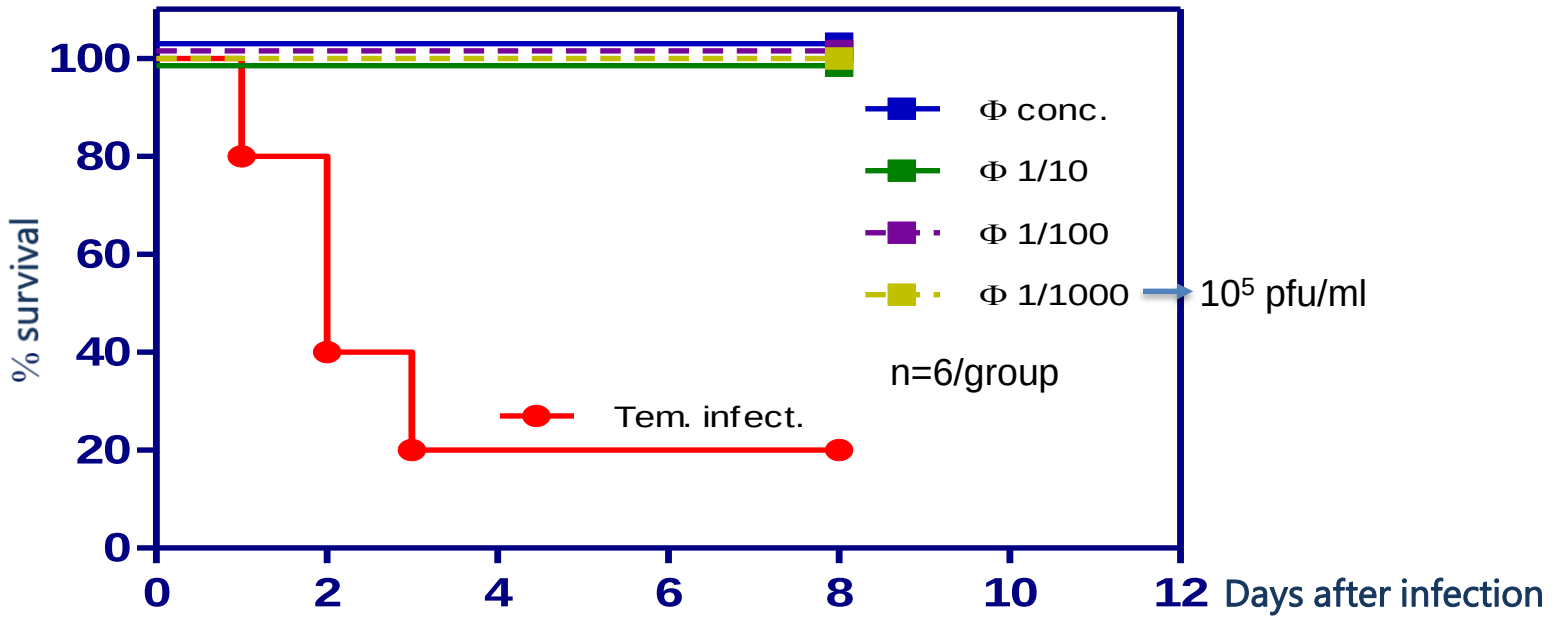
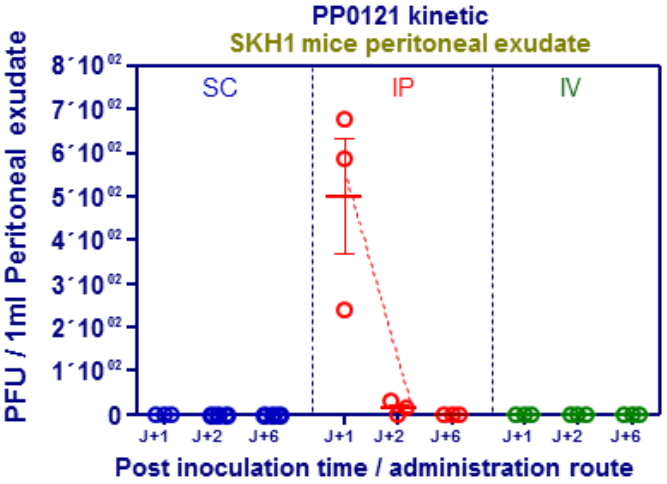
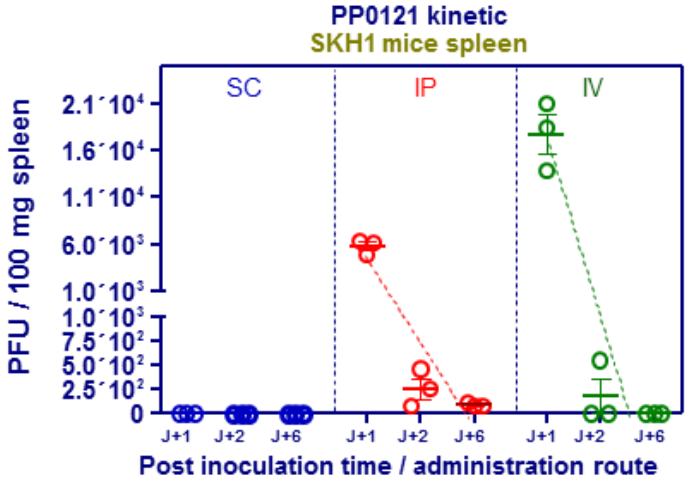
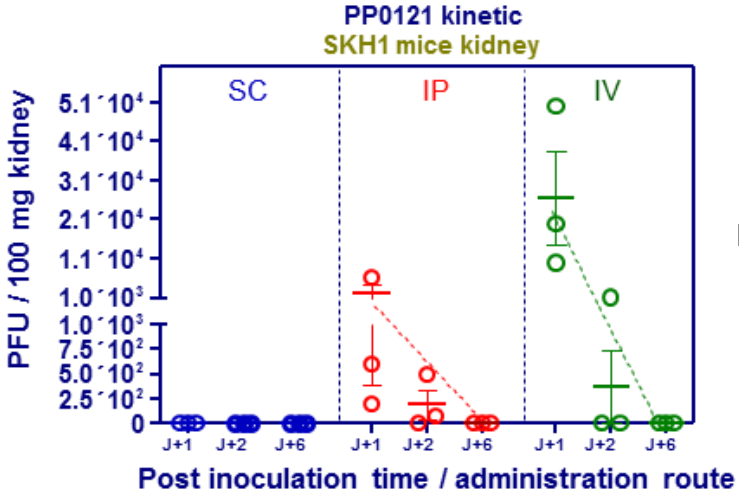


100% efficacy whatever the dilution (1 to 1/1000)

Pharmacokinetics







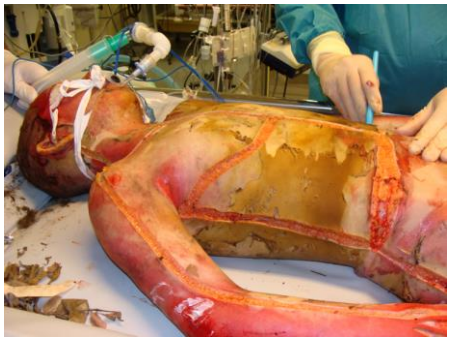
PP0121 injected dose at D0: 10^8 PFU/ml

IV or IP: **phages eliminated** from spleen and kidneys (2 days)
SC: **no phages** detected in mice

THE TUNE

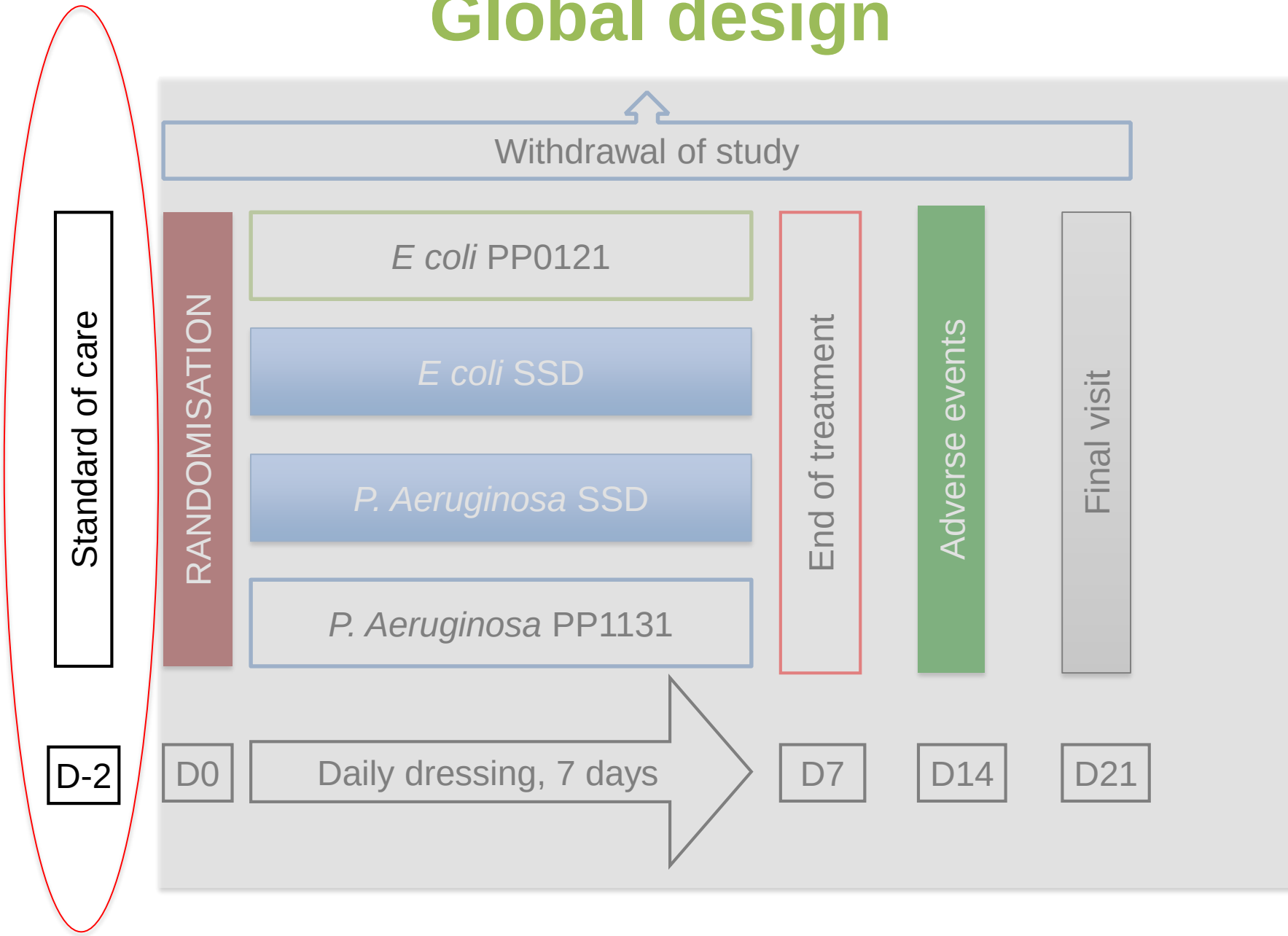
Clinical trial organisation

- Indication: third degree burns infected by *E. coli* or *P. aeruginosa* infections
- International
- Multi centric study
- 220 patients (11 burn centers)
- Hospitalization in intensive care units
- Respect of good medical practices
- Standardization of care +++ (SFETB: French Burn Society)



PhagoBurn

Global design



D-2: preliminary clinical diag.

Clinical suspicion of infection

Bacteriologic sample: Swab

Probabilistic treatment: Povidone iodine (silver free dressing)

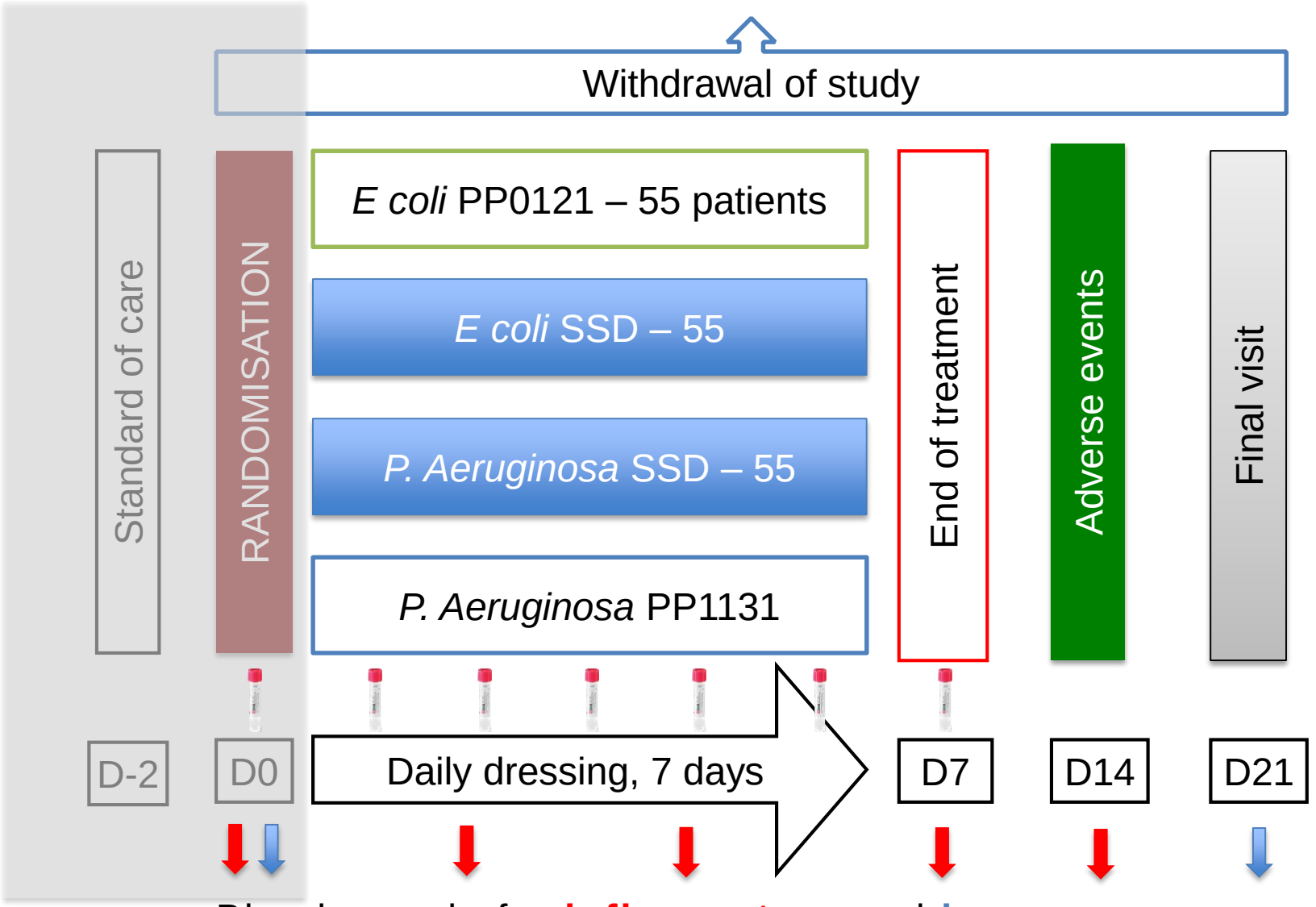
Biological confirmation of bacterial species + antibiogram

Randomization

- Stratification on antibiotics
- Impossible to avoid antibiotic:
  - i.e. patient with both RTI and wound infections
- Antibiotics are free of use
- Consistent to current recommendations

Guidelines for use of antibiotics in burn patient at the acute phase. Ravat F et al. Ann Fr Anesth Reanim. 2009 Mar;28(3):265-74

Global design

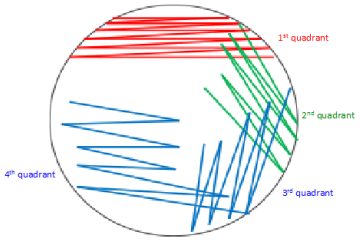


Tested compounds

- Two different phage cocktails:
  - 13 natural lytic phages in PP0121 against *E. coli*
  - 12 natural lytic phages in PP1131 against *P. aeruginosa*
  - Simple buffered water based formulation
- Applied on Algosteril™ bandaid:
  - The only alginate that is authorized for treated deep and 3rd° burn wounds in Europe
  - Manufacturer: Les Laboratoires Brothier
- Standard: 1% Silver sulfadiazine cream:
  - Broad spectrum antiseptic activity: *S. aureus, E coli, P. aeruginosa, Klebsiella sp, Proteus…*
  - But with several known adverse effects

Primary endpoint

- Time for 2 quadrants bacterial reduction relative to D0
  - ➢ A semi quantitative parameter assessed blindly by microbiologists
  - \+ Bacterial species confirmation / identification
  - \+ Antibiogram at the end of phage treatment



- Eswabs from D0 → D8 to collect bacteria according to burn size area for :
  - – Primary endpoint rating & Spp. confirmation by lab centers
  - – Evaluation of wound bacteria response to each DP (cocktail) and to each AS (phage) at Pherecydes lab

THE TEMPO

Adjustments

- Increase duration of project:
  - 1 → 2 years for manufacturing and regulatory approval
- Reduced trial length:
  - From 18 → 11 months
- More investigation centers:
  - From 7 →11 centers and even likely 12
- Adjustment in cocktail:
  - 2 phages dropped in PP0121 and 1 dropped in PP1131
    - bioproduction yield issue
    - phages with similar activity patterns: manufacturing cost reduction
  - Change in final product preparation

Next and ongoing steps

- Safety and management of adverse effects:
  - Provide direct e-crf access to regulatory authorities
  - Data Safety Monitoring Board at trial beginning
- Interactions with inevitable ongoing antibiotics with or without effect on treated strain
- Trial non blind to physicians but blind to assessors (microbiologists)

On 6-8-15 EMA agreed that a cocktail which goes successfully through a phase II trial may “evolve” like vaccines currently do

What did we learn?

- Too many questions to answer in a single study:
  - Safety, efficacy, immune response, phage metabolism, impact of side antibiotic treatments…
- "True" collaborative work is the key:
  - Various Company cultures, medical facilities, regulatory agencies to work together
- No black box with regulatory agencies:
  - Tell the truth and open your files
- Regular information and education of medical crew is critical, including hospital administration

Conclusions

- PHAGOBURN is developed in an Evidence Based Medicine framework
- Efficacy and monitoring of AE of 2 different drugs: PP0121/ PP1131
- Both cocktails sums up to 25 “alive” active substances → 650 CQ tests
- Extrapolation to a « class of drugs »
- Whatever the results, more evidences will be necessary

You want to know more?

- Keep in touch with us on PhagoBurn
  - http://www.phagoburn.eu/
  - https://clinicaltrials.gov/ct2/results?term=bacteriophage&Search=Search
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